

keep all flasks in the same sequence throughout, so that the elapsed time from addition of reagents to reading of fluorescence is the same for each. Carry the test solutions, standard solutions, and the blank through the determination in one group. Add the following three reagents in as rapid a sequence as possible, swirling after each addition, treating 1 flask at a time, in the order named: 1.0 milliliter of ascorbic acid-methanol solution, 3.0 milliliters of concentrated hydrochloric acid, and 1.0 milliliter of hydrogen peroxide-methanol solution. Insert the stoppers in the flasks, and after 2 hours, measure the fluorescence at about 485 millimicrons, using excitation at about 372 millimicrons. In order to provide a check on the stability of the fluorometer, reread one or more standard solutions. Correct each reading for the blank and plot a standard curve of fluorescence versus percentage dissolution. Determine the percentage dissolution of digoxin in the test solutions by reading from the standard graph.

(iv) Digoxin tablets formulated so that the quantity of digoxin dissolved at one hour, when tested by the method in The United States Pharmacopeia (USP XVIII), is greater than 95 percent of the assayed amount of digoxin and so that the quantity of digoxin dissolved at 15 minutes is greater than 90 percent of the assayed amount of digoxin are new drugs which may be marketed only with an approved full new drug application as provided for in §314.50 of this chapter. The application shall include, but not be limited to, clinical studies establishing significantly greater bioavailability than digoxin tablets meeting compendial requirements and dosage recommendations based on clinical studies establishing the safe and effective use of the bioavailable digoxin product. Marketing of these digoxin products will be allowed only under a proprietary or trade name, established name, and labeling which differs from that used for digoxin tablets that meet all of the requirements in The United States Pharmacopeia (USP XVIII) and that are formulated so that either (a) the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed

amount of digoxin or (b) the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin. New drug applications for these digoxin products shall be submitted to the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Drug Evaluation I (HFD-100), 5600 Fishers Lane, Rockville, MD 20857.

[39 FR 11680, Mar. 29, 1974, as amended at 41 FR 43137, Sept. 30, 1976; 41 FR 49482, Nov. 3, 1976; 50 FR 8996, Mar. 6, 1985; 55 FR 11578, Mar. 29, 1990; 65 FR 56479, Sept. 19, 2000]

§310.501 Patient package inserts for oral contraceptives.

(a) *Requirement for a patient package insert.* The safe and effective use of oral contraceptive drug products requires that patients be fully informed of the benefits and the risks involved in their use. An oral contraceptive drug product that does not comply with the requirements of this section is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. Each dispenser of an oral contraceptive drug product shall provide a patient package insert to each patient (or to an agent of the patient) to whom the product is dispensed, except that the dispenser may provide the insert to the parent or legal guardian of a legally incompetent patient (or to the agent of either). The patient package insert is required to be placed in or accompany each package dispensed to the patient.

(b) *Distribution requirements.* (1) For oral contraceptive drug products, the manufacturer and distributor shall provide a patient package insert in or with each package of the drug product that the manufacturer or distributor intends to be dispensed to a patient.

(2) Patient package inserts for oral contraceptives dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first oral contraceptive and every 30 days thereafter, as long as the therapy continues.

(c) *Contents of patient package insert.* A patient package insert for an oral contraceptive drug product is required to contain the following:

(1) The name of the drug.

(2) A summary including a statement concerning the effectiveness of oral contraceptives in preventing pregnancy, the contraindications to the drug's use, and a statement of the risks and benefits associated with the drug's use.

(3) A statement comparing the effectiveness of oral contraceptives to other methods of contraception.

(4) A boxed warning concerning the increased risks associated with cigarette smoking and oral contraceptive use.

(5) A discussion of the contraindications to use, including information that the patient should provide to the prescriber before taking the drug.

(6) A statement of medical conditions that are not contraindications to use but deserve special consideration in connection with oral contraceptive use and about which the patient should inform the prescriber.

(7) A warning regarding the most serious side effects of oral contraceptives.

(8) A statement of other serious adverse reactions and potential safety hazards that may result from the use of oral contraceptives.

(9) A statement concerning common, but less serious side effects which may help the patient evaluate the benefits and risks from the use of oral contraceptives.

(10) Information on precautions the patients should observe while taking oral contraceptives, including the following:

(i) A statement of risks to the mother and unborn child from the use of oral contraceptives before or during early pregnancy;

(ii) A statement concerning excretion of the drug in human milk and associated risks to the nursing infant;

(iii) A statement about laboratory tests which may be affected by oral contraceptives; and

(iv) A statement that identifies activities and drugs, foods, or other substances the patient should avoid because of their interactions with oral contraceptives.

(11) Information about how to take oral contraceptives properly, including information about what to do if the pa-

tient forgets to take the product, information about becoming pregnant after discontinuing use of the drug, a statement that the drug product has been prescribed for the use of the patient and should not be used for other conditions or given to others, and a statement that the patient's pharmacist or practitioner has a more technical leaflet about the drug product that the patient may ask to review.

(12) A statement of the possible benefits associated with oral contraceptive use.

(13) The following information about the drug product and the patient package insert:

(i) The name and place of business of the manufacturer, packer, or distributor, or the name and place of business of the dispenser of the product.

(ii) The date, identified as such, of the most recent revision of the patient package insert placed prominently immediately after the last section of the labeling.

(d) *Other indications.* The patient package insert may identify indications in addition to contraception that are identified in the professional labeling for the drug product.

(e) *Labeling guidance texts.* The Food and Drug Administration issues informal labeling guidance texts under § 10.90(b)(9) of this chapter to provide assistance in meeting the requirements of this section. A request for a copy of the guidance texts should be directed to the Center for Drug Evaluation and Research, Division of Metabolism and Endocrine Drug Products (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(f) *Requirement to supplement approved application.* Holders of approved applications for oral contraceptive drug products that are subject to the requirements of this section are required to submit supplements under § 314.70(c) of this chapter to provide for the labeling required by this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[54 FR 22587, May 25, 1989]